World Health Organization

Guideline:

Intermittent iron supplementation in preschool and school-age children

WHO Library Cataloguing-in-Publication Data

Guideline: Intermittent iron supplementation in preschool and school-age children.

1.Iron – administration and dosage. 2.Anaemia, Iron-deficiency – prevention and control. 3.Child, Preschool. 4.Child. 5.Dietary supplements. 6.Guidelines. I.World Health Organization.

ISBN 978 92 4 150200 9 (NLM classification: WH 160)

Design and layout: Alberto March

Suggested citation

WHO. *Guideline: Intermittent iron supplementation in preschool and school-age children.* Geneva, World Health Organization, 2011.

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Acknowledgements

This guideline was coordinated by Dr Luz Maria De-Regil under the supervision of Dr Juan Pablo Peña-Rosas, with technical input from Dr Metin Gulmezoglu, Dr Jose Martines, Dr Matthews Mathai and Dr Lisa Rogers. Thanks are due to Dr Regina Kulier and the staff at the Guidelines Review Committee Secretariat for their support throughout the process. Thanks to also due to Dr Davina Ghersi for her technical advice and assistance in the preparation of the technical consultations for this guideline and Mr Issa T. Matta and Mrs Chantal Streijffert Garon from the World Health Organization (WHO) Office of the Legal Counsel for their support in the management of conflicts of interest procedures. Ms Grace Rob and Mrs Paule Pillard from the Micronutrients Unit, Department of Nutrition for Health and Development, provided logistic support.

WHO gratefully acknowledges the technical input of the WHO Nutrition Steering Committee and the Nutrition Guidance Expert Advisory Group (NUGAG), especially the chairs of the meetings, Dr Janet King, Dr Rebecca Stoltzfus and Dr Rafael Flores-Ayala. WHO is also grateful to the Cochrane Developmental, Psychosocial and Learning Problems Group staff for their support during the development of the systematic review used to inform this guideline.

Financial support

WHO thanks the Government of Luxembourg for providing financial support for this work.

WHO Guideline[1]

Intermittent iron supplementation in preschool and school-age children

Summary

It is estimated that 600 million preschool and school-age children worldwide are anaemic, and it is assumed that at least half of these cases are attributable to iron deficiency. Member States have requested guidance from the World Health Organization (WHO) on the effects and safety of intermittent iron supplementation in children as a public health intervention to improve their iron status and reduce the risk of developing iron deficiency anaemia, in support of country efforts to achieve the Millennium Development Goals.

WHO has developed the present evidence-informed recommendations using the procedures outlined in the *WHO handbook for guideline development*. The steps in this process included: (i) identification of priority questions and outcomes; (ii) retrieval of the evidence; (iii) assessment and synthesis of the evidence; (iv) formulation of recommendations, including research priorities; and (v) planning for dissemination, implementation, impact evaluation and updating of the guideline. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was used to prepare evidence profiles related to preselected topics, based on up-to-date systematic reviews.

The guideline development group for nutrition interventions, the Nutrition Guidance Expert Advisory Group (NUGAG), comprises content experts, methodologists, representatives of potential stakeholders and consumers. These experts participated in several WHO technical consultations concerning this guideline, held in Geneva, Switzerland, and Amman, Jordan, in 2010 and 2011. Members of the External Experts and Stakeholders Panel were identified through a public call for comments, and this panel was involved throughout the guideline development process. NUGAG members voted on the strength of the recommendation, taking into consideration: (i) desirable and undesirable effects of this intervention; (ii) the quality of the available evidence; (iii) values and preferences related to the intervention in different settings; and (iv) the cost of options available to health-care workers in different settings. All NUGAG members completed a Declaration of Interests Form before each meeting.

In settings where the prevalence of anaemia in preschool or school-age children is 20% or higher, intermittent use of iron supplements is recommended as a public health intervention to improve iron status and reduce the risk of anaemia among children (strong recommendation). In comparison with a placebo or no intervention, the overall quality of the available evidence was found to be moderate for anaemia, low for haemoglobin and ferritin concentrations and very low for iron deficiency. When compared with daily supplementation, the quality of the available evidence for intermittent supplementation with regard to anaemia and haemoglobin and ferritin concentrations was found to be low and for iron deficiency it was very low.

[1] A WHO guideline is any document, whatever its title, containing WHO recommendations about health interventions, whether they be clinical, public health or policy interventions. A recommendation provides information about what policy-makers, health-care providers or patients should do. It implies a choice between different interventions that have an impact on health and that have ramifications for the use of resources. All publications containing WHO recommendations are approved by the WHO Guidelines Review Committee.

Scope and purpose

This guideline provides global, evidence-informed recommendations on the intermittent use of iron supplements for preschool and school-age children as a public health intervention to improve iron status and reduce the risk of childhood iron deficiency anaemia.

The guideline will help Member States and their partners in their efforts to make informed decisions on the appropriate nutrition actions to achieve the Millennium Development Goals, in particular, the eradication of extreme poverty and hunger (MDG 1), achievement of universal primary education (MDG 2) and reduction of child mortality (MDG 4). The guideline is intended for a wide audience including policy makers, their expert advisers, and technical and programme staff at organizations involved in the design, implementation and scaling-up of nutrition actions for public health.

This document presents the key recommendation and a summary of the supporting evidence. Further details of the evidence base are provided in Annex 1 and other documents listed in the references.

Background

Iron deficiency, a common form of nutritional deficiency during childhood, results from sustained negative iron balance, which is caused by inadequate dietary intake, absorption or utilization of iron, increased iron requirements during the growth period, or blood loss due to parasitic infections such as malaria, soil-transmitted helminth infestations and schistosomiasis. In later stages of iron depletion, the haemoglobin concentration decreases, resulting in anaemia. Anaemia is characterized by a reduction in the oxygen-carrying capacity of blood, such that the physiological oxygen needs of the affected individual can no longer be met. In addition to iron deficiency, other micronutrient deficiencies (e.g. folate, vitamin B_{12} and vitamin A), chronic inflammation and inherited disorders of haemoglobin structure can all cause anaemia (*1*). Diagnosis of anaemia requires measurement of the haemoglobin concentration, while serum ferritin and serum soluble transferrin receptor levels are commonly used as indicators of iron status. A diagnosis of iron deficiency anaemia is made when there is both anaemia and iron deficiency (*2*).

Children are particularly vulnerable to iron deficiency anaemia because of their increased iron requirements in the periods of rapid growth, especially in the first 5 years of life. It is estimated that worldwide, 600 million preschool and school-age children are anaemic, and it is assumed that at least half of these cases are attributable to iron deficiency (*3*). Iron deficiency anaemia in children has been linked to increased childhood morbidity and impaired cognitive development and school performance. Both epidemiological and experimental data suggest that when these impairments occur at an early age, they may be irreversible, even after repletion of iron stores, thus reinforcing the importance of preventing this condition (*4, 5*).

Public health interventions to ameliorate micronutrient malnutrition in preschool and school-age children include the promotion of dietary diversification to include foods rich in highly absorbable vitamins and minerals, anthelminthic treatment, mass fortification of staple foods and condiments, home (point of use) fortification of foods, and provision of micronutrient supplements (*6*). The effectiveness of such interventions in these age groups is variable and not always aimed at meeting children's needs (for example, in the case of mass fortification) whereas in other cases the interventions are not feasible because of economic or behavioural constraints (*7*). Although daily iron supplementation has proven to be effective in increasing haemoglobin concentrations in children, especially in those who are anaemic (*8*), in real-world settings, the low coverage rates and insufficient tablet distribution, the prolonged duration of the intervention and the associated side-effects (e.g. gastrointestinal discomfort, constipation and staining of teeth with drops or syrups) may limit adherence to the intervention, especially in young children (*7*, *9*).

Intermittent use of oral iron supplements (i.e. once, twice or three times a week on non-consecutive days) has been proposed as an effective alternative to daily iron supplementation to prevent anaemia among children (*10, 11*). The proposed rationale behind this intervention is that intestinal cells turn over every 5–6 days and have limited iron absorptive capacity. Thus intermittent provision of iron would expose only the new epithelial cells to this nutrient, which should, in theory, improve the efficiency of absorption (*12, 13*). Intermittent supplementation also may minimize blockage of absorption of other minerals due to the high iron levels in the gut lumen and in the intestinal epithelium (*14*). This overall reduced exposure to iron is particularly relevant in malaria settings (where it has been suggested that the provision of additional iron may exacerbate the infection) as less iron may be available for the parasite's growth (*15*). Experience in different populations has shown that intermittent regimens reduce the frequency of other side-effects associated with daily iron supplementation and are also more acceptable to recipients, thus increasing compliance with supplementation programmes (*16*).

Summary of evidence

A Cochrane systematic review (*17*) was conducted to assess the effects and safety of intermittent iron supplementation alone or in combination with other micronutrients inchildren under 12 years of age with regard to health and nutrition outcomes. The review compared the provision of iron supplements on an intermittent basis versus no intervention or placebo, and versus daily use of iron supplements, among children living in a variety of settings, including malaria-endemic areas.

The outcomes considered to be critical for decision-making by the Nutrition Guidance Expert Advisory Group (NUGAG) were anaemia, haemoglobin concentration, iron status and mortality. The potential modifying effects of the baseline anaemia prevalence, total iron dose per week, the intermittent regimen scheme, duration of the intervention, supplement formulation and sex were also assessed.

The review included 33 randomized controlled trials involving 13 144 children from 20 countries in Latin America, Africa and Asia where anaemia prevalence was moderate to high. Most of the trials used ferrous sulfate as the iron source, with doses ranging from 7.5 mg to 200 mg of elemental iron per week. In five studies, iron was given in combination with folic acid, in doses that ranged from 100 µg (0.1 mg) to 500 µg (0.5 mg) per week.

Compared with placebo or no intervention, intermittent iron supplementation (alone or in combination with other nutrients) in children younger than 12 years of age significantly increased the concentration of haemoglobin (mean difference (MD) 5.20 g/l, 95% confidence interval (CI) 2.51–7.88, 19 studies) and ferritin (MD 14.17 µg/l, 95% CI 3.53–24.81, five studies), and reduced the risk of presenting anaemia at the end of the intervention (relative risk (RR) 0.51, 95% CI 0.37–0.72, 10 studies).

On the other hand, compared with children receiving daily iron supplements, those receiving iron supplements intermittently were more likely to be anaemic at the end of the intervention (RR 1.23, 95% CI 1.04–1.47, six studies) but the mean difference in the haemoglobin and ferritin concentrations between the two groups was not significant (MD –0.60, g/l 95% CI –1.54 to 0.35, 19 studies, and –4.19 µg/l, 95% CI –9.42 to 1.05, 10 studies, respectively). Adherence tended to be higher among children receiving intermittent supplementation compared with those receiving daily supplementation, although this result was not statistically significant.

The micronutrient composition of the supplements (iron alone, iron plus folic acid, or iron plus other micronutrients) did not impact on the above findings, although most of the evidence was derived from trials using supplements containing only iron. In addition, the intervention seemed efficacious in settings with different baseline prevalence of anaemia, in both sexes, across trials lasting either less or more than 3 months and with all intermittent regimens.

No deaths were reported in the trials. Although limited data were available on outcomes related to morbidity, neurocognitive outcomes, other indicators of vitamin and mineral status, and side-effects, no evidence was found of increased morbidity or side-effects, including in malaria-endemic settings.